ARTICLE

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Prevention of Non Communicable Diseases

Association of the Healthy Nordic Food Index with risk of bladder cancer: a case–control study

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BACKGROUND: Bladder cancer (BC) is the ninth recurrent neoplasm in the world. In Iran, incidence of BC is the third most common among men. Few dietary patterns are related to reduced carcinogenesis and consequently are amenable to modification in order to reduce the BC risk. Adherence to the traditional Nordic diet, as measured by the Healthy Nordic Food Index (HNFI), have shown a beneficial effect on chronic disease prevention, including cancer. The principal objective of this study was to investigate the association between HNFI and the odds of BC in a case-control study, in Iran.

METHOD: The present case-control study was performed on 100 eligible cases and 200 controls of patients ≥45 years old referred to three referral hospitals in Tehran. Dietary intakes are assessed by a valid 168-item food frequency questionnaire (FFQ). The relationship between HNFI and BC is estimated using the logistic regression tests.

RESULTS: The average age of cases and control were 65.41 and 61.31 years, respectively. After controlling for potential confounders (age, smoke, total energy, and sex), participants in the highest tertile of HNFI (compared to the lowest tertile) have 83% lower BC risk (OR = 0.17; 95%CI = 0.07–0.42). Based on an independent assessment of HNFI component and BC risk, a significant negative association was observed for fish intake (OR = 0.30; 95%CI = 0.15– 0.60) and whole-grain bread intake (OR = 0.33; 95%CI = 0.17–0.63).

CONCLUSION: The findings of this study suggested that adherence to traditional Nordic diet could decrease the risk of BC. Of the elements of this diet, fish and whole-grain bread consumption seemed to decrease the odds of BC. Such findings ought to be considered in the development of evidence-base intervention for BC prevention in the country.

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BACKGROUND

Bladder cancer (BC) is the ninth most common cancer in the world [1]. The incidence of BC is about 1.5 to 6.6 per 100.000 people worldwide [2] while more than 900.000 new BC cases and 250.000 BC deaths are reported worldwide each year [3]. A total of 148.568 cases of BC were diagnosed in Asian country in 2012 [2]. In Iran, the incidence of BC is about 13.03 and 3.32 per 100.000 in men and women, respectively and it is the third most common cancer in men [4]. Age, masculine sex, smoking, bladder infection with Schistosoma haematobium, exposure to aromatic hydrocarbon and aromatic amines, particular drugs, and genetic factors are some of the well-studied risk factors of BC [5]. It is suggested that the quality of diet might affect some BC carcinogenic factors and therefore causes a preventive effect [6]. A significant positive association was observed between western dietary pattern and bladder cancer, which is suggested the role of diet in etiology of bladder cancer [7]. One index for assessing diet quality is the Healthy Nordic Food Index (HNFI), which includes items from the traditional Nordic diet with beneficial health effects [8]. The traditional Nordic diet included unhealthy items like sugar, red meat, and full-fat dairy, but HNFI consists of six food items (fish, cabbages, barley, whole-grain bread, apples and pears, and root vegetables) which have health-enhancing effects [9]. Adherence to HNFI decreased the odds of colorectal cancer by 9% in women [10]. A significant negative association between HNFI and cancer mortality has been observed in a few prior investigations [11–13]. In addition, contrast results were observed between adherence to HNFI and colorectal cancer incidence [10, 14, 15]. Previous studies have indicated the beneficial effects of traditional Healthy Nordic Food items on BC prevention [16–21]. Due to accessibility of HNFI items in Iran and the beneficial effects of HNFI in cancer prevention, we decide to assess HNFI in this study. To our knowledge, there are no data to clarify whether adherence to HNFI may reduce the risk of BC. Therefore, the main aim of this

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study was to explore the hypothetical role of HNFI in preventing the BC in Iran.

METHODS

Study design and sampling

Our study is a hospital-based case–control study conducted at three referral hospitals in Tehran (the capital of Iran), between December 2018 and March 2020. Cases included 100 patients ≥45 years old who had been newly diagnosed (<6 months) with BC (mostly transitional cell carcinoma). Among cases, 63% of cancers were non-invasive (NMIBC, Ta/T1) and 37% were muscle-invasive (MIBC, other T). The exclusion criteria applied for cases were: following the specific type of diet, history of other types of cancer and received previous chemotherapy or radiotherapy before enrollment. The control group consisted of 200 patients of similar age, from the same hospitals, and they were selected from a wide spectrum of non-neoplastic diseases unrelated to smoking, and long term diet modification (e.g., trauma, orthopedic conditions, disk disorders, acute surgical conditions and eye, nose, ear, or skin disorders). The exclusion criteria applied for controls were: have neoplastic diseases with relation with smoking and long term diet modification. All patients in both groups were interviewed during hospital admission. New patients were interviewed during hospital admission and old patients interviewed when they came to hospital for control visits. We used the same order for controls.

All cases were confirmed histologically on tumor tissue specimens from surgery or biopsy. The protocol followed in this study was carried out in accordance with the guidelines laid down in the Helsinki Declaration and all steps related to human subjects were approved by the National Nutrition and Food Technology Research Institute of Iran. All patients provided a written consent form before participation.

Ethics

The research ethics certification was IR.SBMU.NNFTRI.REC.1398.010.

Dietary assessment

In a face-to face interview, trained personnel administered the questionnaires to participants during their stay in the hospital. The dietary intake was assessed by a 168-item Food Frequency Questionnaire (FFQ) that is validated in Iran [20]. Patients were asked about the frequency of consumption of each food item on a daily, weekly, monthly, and annual basis. Energy intake was calculated using the USDA Food Composition Table. Traditional Iranian foods that were not in the USDA database were calculated from the Iranian Food Composition Table.

Assessment of non-dietary exposure

Socio-demographic, lifestyle and clinical information of the participants were collected using a questionnaire including information about age (years), family history of BC (yes, no), education (step-wise education levels from illiterate to university graduation), current smoker (yes, no), history of cancer (yes, no), diabetes (yes, no), hyperlipidaemia (yes, no), cardiovascular disease (yes, no), marital status (single, married, divorced or widow, widower) and supplement intake including: iron, calcium, zinc, B complex (yes, no). In addition, physical activity over the past 7 days was evaluated by a valid questionnaire that assessed physical activity [22], and its level was quantified in terms of Met.min/week [22]. Individual's weight, while clothed lightly, was measured with the precision of 1 kg using a digital scale (Seca, Hamburg, Germany). Height was measured to the nearest 0.5 cm by a non-stretchable tape. Body Mass Index (BMI) was calculated as the ratio of weight (kg) to height squared (m^2).

HNFI calculation

HNFI is originally developed by Olsen et al. [8] and contains only foods with the beneficial effect of a traditional Nordic Diet [8]. The six HNFI food items in our study are fish, cabbages, barley, whole-grain bread, apples and pears, and root vegetables. The sex-specific, median intake of each component in HNFI was calculated. Then, one point per component was given to each individual who consumed more than this median value, and the total HNFI score was calculated by adding up these points. This procedure resulted in a score that ranges from 1 to 6 [8].

Statistical analysis

Statistical tests were performed using SPSS software version 21.0 (SPSS Inc., Chicago, IL). The Kolmogorov–Smirnoff test was conducted to examine the normality of the distribution of the variables. Mean values of cases and controls were compared using the Student's t-test and the means of more than two groups were assessed using Analysis of Variance for normal distribution variables. Also, nonparametric statistics, including the Mann–Whitney *U* test or Kruskal–Wallis test were used for variables that were not normally distributed. Chi-square was used for categorical variables to compare characteristics of cases and controls. Age, sex, total energy intake, and smoking were determined as covariates and all models were adjusted for these confounders. The variables level of BMI, physical activity, education, drugs, supplement use, family history of BC, and other factors were initially included in all models but since the results did not change appreciably, these variables were not included in the final models. HNFI was analyzed as tertile. Binary logistic regression was implemented to estimate odd ratios (ORs) and 95% confident intervals (CIs) adjusted for multiple covariates in different models.

RESULTS

The sociodemographic and lifestyle characteristics of participants are presented in Table 1. Compared to the first tertile of HNFI only in controls, participants in the highest tertile were more likely to

Table 1. Characteristics of participants ($n = 300$) across the Healthy Nordic Food Index (HNFI) tertile categories in case–control study of bladder cancer in Iran.

	Bladder cancer cases HNFI tertile $n = 100$			*p* Trend[a]	Controls HNFI tertile $n = 200$			*p* Trend[a]	*p* value[b]
	1 ($n = 62$)	2 ($n = 28$)	3 ($n = 10$)		1 ($n = 85$)	2 ($n = 59$)	3 ($n = 56$)		
HNFI, range[c]	1-3	4	5-6		1-3	4	5-6		
Age (year)	66.2 ± 9.6	64.7 ± 10.6	65.4 ± 11.0	0.678	59.9 ± 13.2	65.2 ± 17.4	62.9 ± 12.5	0.052	0.004
Male, *n*(%)	55(88.7)	24(85.7)	10(100)	0.994	41(48.2)	28(47.4)	24(42.8)	0.993	<0.001
BMI[a] (kg/m^2)	24.6 ± 4.2	25.2 ± 4.3	24.6 ± 3.8	0.422	26.9 ± 5.4	23.4 ± 4.3	24.0 ± 4.1	0.175	0.148
Physical activity[d] (met.min/week)	58.1 ± 322.1	16.5 ± 89.1	54.0 ± 170.7	0.096	14.1 ± 93.3	18.3 ± 140.6	182.5 ± 729.1	0.878	0.334
University education, *n* (%)	0	0	2(3.5)	0.997	4(3.7)	0	3(3.7)	0.003	0.338
Current smoker, *n* (%)	40(64.5)	15(53.5)	8(80.0)	0.269	8(9.4)	10(16.9)	7(12.5)	0.405	<0.001

BMI body mass index.
[a]*The p* value for trend was determined using linear regression coefficient for HNFI for continuous variables and logistic regression for nominal variable.
[b]The *p* value for comparing variables in cases and controls. For continuous variables, independent *t* test was used for variable with normal distribution and Mann-Whitney was used for variables that were not normally distributed. Chi-square or Fisher-test were used for categorical variables.
[c]Possible point ranges from 1 to 6.
[d]The Metabolic Equivalent of Task is evaluated by International Physical Activity Questioner (IPAQ).

have higher education (university graduation). There were no significant differences across the tertile of HNFI for other variables (Table 1).

When HNFI expressed as tertiles (Table 2), being in the highest tertile of HNFI (compare to lowest tertile.) could decrease the odd of BC by 77% in the crude model (OR = 0.23; 95%CI: 0.11–0.50). Subsequent to controlling for age, sex and smoking as confounders in model 1, HNFI decreased the risk of BC by 74% (OR = 0.26; 95%CI: 0.11–0.58; p trend = 0.001) (Table 2). After adding the total energy intake as a confounder in model 2, an even stronger negative association was observed between adherence to HNFI and risk of BC (OR = 0.17; 95%CI = 0.07–0.42; p trend < 0.001).

Table 2. Odd ratio of bladder cancer by tertile of Healthy Nordic Food Index(HNFI) in a case–control study in Iran.

Score	Crude OR (95% CI)	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)
HNFI			
t1(1–3)	1.00(Reference)	1.00(Reference)	1.00(Reference)
t2(4)	0.65(0.37–1.13)	0.66(0.36–1.20)	0.51(0.27–0.97)*
t3(5–6)	0.23(0.11–0.50)*	0.26(0.11–0.58)*	0.17(0.07–0.42)*
P trend	0.001	0.004	<0.001

*P value < 0.05.
[a]Values are adjusted for age, sex and smoking.
[b]Values are adjusted for age, sex, smoking, and total-energy.

Table 3. Multivariate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for comparing the components of Healthy Nordic Food Index (HNFI) in odds of bladder cancer, Iranian bladder cancer case–control study[a,b].

Food items[c] (g/day)	Multivariate Adjusted Bladder Cancer Risk		
	OR	95% CI	p
Apple and pear	1.78	0.52–6.11	0.358
Root vegetable	1.84	0.83–0.04	0.129
Cabbage	1.03	1.00–1.05	0.228
Whole grain bread	0.33	0.17–0.63	0.001
Barley	0.69	0.40–1.17	0.175
Fish	0.30	0.15–0.60	0.001

[a]Values are adjusted for age, sex, total energy intake and smoking.
[b]Variables were considered as continuous variables.
[c]Odds ratio was calculated per one-point increase of food items.

By examining the association between six components of HNFI and BC (Table 3), significant negative associations were observed just for fish and whole-grain bread intake (P value < 0.05).

Compared to the cases, consumption of all six components of HNFI (fish, cabbages, barley, whole-grain bread, apples and pears, and root vegetables) were higher in controls (Table 4). The correlation coefficient between the total HNFI and its individual components was the lowest for the cabbage (0.18 in bladder cases vs. 0.24 in controls) and highest for root vegetables (0.46 in bladder cases vs. 0.61 in controls) and fish (0.50 in bladder cases vs. 0.49 in controls) (Table 4).

DISCUSSION

The findings from present study showed that dietary patterns of Iranian population deviate from HNFI, the mean HNFI in this population was almost one–half of the maximum score, which showed less consumption of HNFI components in this population. The present study showed that HNFI was negatively associated with the risk of BC. Among HNFI components, intake of fish and whole-grain bread were related to a reduced risk of BC.

Several studies have investigated Nordic dietary patterns as health-enhancing Nordic diet [23], New Nordic Diet (NND) [24], and HNFI [8]. Different studies have tailored Nordic diet for regional conditions and consisted of different components, e.g., fish/shellfish, oats, cabbages, root vegetables, apples and pears, berries, whole grain rye, rapeseed oil, and low-fat dairy [8, 23–27]. Since the consumption of some of the NND items, e.g., native Nordic berries and rapeseed oil is not common in Iran, we measured HNFI due to the availability of its components in our country.

To our knowledge, this research represents the first study that evaluated the relationship between HNFI and BC risk. Previous studies have revealed a significant negative association between HNFI and cancer mortality [11–13]. A systematic review of the association between HNFI and all kinds of cancers [28] showed that adherence to HNFI was related to a 9% reduction in the risk of colorectal cancer [10] and 11% improvement in colorectal cancer survival [29]. In the present study, fish and whole-grain bread scores were negatively correlated with odds of BC. In line with our study, an Italian study examining the association between the Mediterranean Diet Score and the risk of BC, observed an inverse relationship between fish consumption and BC risk [30]. In addition, another study observed this inverse relation in none-smoker men [31]. The preventive effect of fish may be attributed to anti-inflammatory effect [31]. Chronic inflammation induces tumor development by promoting tissue and DNA damage and altering cell growth [31]. Persistent bladder infection or enlarged prostate gland increases the contact of carcinogens with the bladder epithelial and leads to chronic inflammation and cancer

Table 4. Dietary intake distribution and Spearman rank correlation of Healthy Nordic Food Index in a case–control study of bladder cancer in Iran.

Food items	Bladder cancer cases		controls	
	Intake distribution[a] (g/day)	Spearman Rank correlation[b]	Intake distribution[a] (g/day)	Spearman Rank correlation[b]
Cabbage	1.0(0.4–1.6)	0.178	0.5(0.1-53.0)	0.242
Fish	3.6(0.0–44.0)[c]	0.505	4.0(0.0–21.0)	0.491
Barley	0.6(0.0–19.7)	0.455	1.0(1.0–8.6)	0.562
Root vegetable	5.7(0.0–74.7)	0.460	10.9(0.0–51.6)	0.609
Apple and pear	70.7(1.2– 198.0)	0.312	80.4(0.0–364.0)	0.255
Whole grain bread	3.3(0.0– 415.0)[a]	0.496	26.3(0.0–276.0)	0.491

[a]Data are median (5th, 95th percentile).
[b]Correlations between food items and total HNFI.
[c]Statistically significant between bladder cancer cases and controls (p < 0.05).

development [31]. Whole-grain bread and other components of HNFI are rich in fiber. Dietary fiber carries out an important role in regulating blood glucose, lowering blood insulin, reducing inflammatory factors, cutting oxidative stress, and metabolic regulation, which supports the protective role of fiber in BC prevention [20]. In this research, fruit and vegetable score were unrelated to the risk of BC, which could be a result of the low variety of fruit and vegetables in HNFI.

The HNFI components are rich in vitamins C, K, folate, iron, dietary fiber, and other bioactive components that can prevent chronic diseases including cancer [28, 29]. Cabbages as cruciferous vegetables have anticarcinogenic effects. Tang et al have reported that raw cruciferous vegetables such as cabbage, broccoli, flower cabbage decrease the risk of BC by 57–68% [18]. Cruciferous vegetables are rich in isothiocyanate and, dietary isothiocyanate and its urinary metabolites showed an anti-proliferative effect on human bladder cells at in vivo [18]. Vitamin C, folic acid, carotenoids, iodine, fiber, and selenium content of cruciferous vegetables cause anticarcinogenic effects [18]. Root vegetables in HNFI especially carrots are rich in carotenoids, the antioxidant effect of Carotenoids, β-carotene inhibits oxidative damage of DNA and inhibits the carcinogenesis in bladder cell [16, 19, 21]. Another study indicated an inverse association between plasma and dietary β-carotene and invasive BC, although this association was not observed in none invasive BC [19]. The risk of developing BC in smokers with higher plasma carotenoid is low [19]. In addition, carotenoids as a precursor to vitamin A play a vital role in regulating cell proliferation [17, 19]. Present study showed no association between consumption of cabbage and root vegetables and odds of BC. It might be due to low intake of cabbage and root vegetables among the participants.

The strengths of this study include the use of valid tools and questionnaires, the use of newly incident cases (<6 months diagnosis), and administrating FFQ by trained interviewers. Selection bias was minimized with a high participation rate (more than 95%) and with the selection of hospital controls from patients whose admission diagnosis was unrelated to smoking and diet-related diseases. We used the identical questionnaires for both cases and controls in similar conditions to reduce information bias. This is the first case–control study in the world to evaluate HNFI in BC risk. A possible limitation of this study remains the fact that some items like oat and rye in the original format of HNFI were replaced with barley and whole-grain bread because of rare consumption in Iranian food culture. Another probable limitation are recall-bias. Other limitations were relatively small sample size, not assessing occupational exposures. Furthermore, there were big difference in gender (male gender ≈80% vs. ≈40%) and smoking (≈60% vs. ≈15%) between BC patients and controls. Even if multivariate analysis adjusted for these variables, the high difference could confound the results.

In conclusion, we found that adherence to HNFI could significantly decrease the BC risk. Among the components of HNFI, a significant association was observed between fish and whole-grain bread consumption and the risk of BC. Isothyociante, fiber, and anti-oxidant content of HNFI component might represent the potential protective factors against BC. Further investigations, especially cohort studies, are recommended to confirm these findings.

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AUTHOR CONTRIBUTIONS

MH, Writing the draft, study design, analysis. AR, Nutrition consultation and analysis. FA, English editing. MKP, Urology consultation. MA, Oncology consultation. SJ, editing the draft. BR, Study design and corresponding author.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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